The Hippo pathway in organ size control, tissue regeneration and stem cell self-renewal.

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Public Summary:
The Hippo pathway in organ size control, tissue regeneration, and stem cell self-renewal Precise control of organ size is crucial during animal development and regeneration. In the past decade, studies have uncovered a critical role of the Hippo tumor-suppressor pathway in the regulation of organ size. The function of the Hippo pathway in organ size control is highly conserved from fruit fly to human. The Hippo pathway limits organ size by inhibiting cell proliferation and increasing cell death, leading a decrease of cell numbers. Therefore, the Hippo pathway negatively inhibits organ growth. Function of the Hippo pathway has also been implicated in human cancer. Mutation (inactivation) of this pathway leads to massive tissue overgrowth and tumor development. The major function of the Hippo pathway is to inhibit the activity of YAP, which is a transcription co-activator and an oncogene. YAP itself cannot bind DNA but is able to stimulate gene expression by binding to DNA binding transcription factors. YAP can stimulate cell proliferation and inhibit cell death. Therefore, high YAP activity stimulates cancer development. Recent works from our laboratory have established an important function of YAP in embryonic stem cell maintenance. Artificial inactivation of YAP activity causes differentiation of stem cells while artificial activation of YAP promotes induction of induced pluoripotent stem cells. The Hippo pathway also plays a critical role in the self-renewal and expansion of stem cells and tissue-specific progenitor cells, and has important functions in tissue regeneration. Hippo pathway is inhibited during tissue regeneration. Recent studies have also shown that TAZ, which is a gene has similar function as YAP and is also inhibited by the Hippo pathway, is essential for the maintenance of breast cancer stem cells. These data support a critical role of the Hippo pathway in cancer. Emerging evidence shows that the Hippo pathway is regulated by cell polarity, cell adhesion, and cell junction proteins. In fact, the Hippo pathway is controlled by cell contact. When cells contact each other, the Hippo pathway activity is increased and the high Hippo activity inhibits cell growth. This cell contact signals might be mediated by tight junction and adherence junction. Therefore, the Hippo pathway may sense the presence of neighbors (cell density) to determine whether cells should continue to grow or not. When cell density is high, the Hippo pathway is activated and cell growth will be stopped. When cell density is low, the Hippo pathway is inhibited, so cell growth is permitted. This may explain how the Hippo pathway is involved in organ size regulation, by sensing the presence of neighbors.

Scientific Abstract:
Precise control of organ size is crucial during animal development and regeneration. In Drosophila and mammals, studies over the past decade have uncovered a critical role for the Hippo tumour-suppressor pathway in the regulation of organ size. Dysregulation of this pathway leads to massive overgrowth of tissue. The Hippo signalling pathway is highly conserved and limits organ size by phosphorylating and inhibiting the transcription co-activators YAP and TAZ in mammals and Yki in Drosophila, key regulators of proliferation and apoptosis. The Hippo pathway also has a critical role in the self-renewal and expansion of stem cells and tissue-specific progenitor cells, and has important functions in tissue regeneration. Emerging evidence shows that the Hippo pathway is regulated by cell polarity, cell adhesion and cell junction proteins. In this review we summarize current understanding of the composition and regulation of the Hippo pathway, and discuss how cell polarity and cell adhesion proteins inform the role of this pathway in organ size control and regeneration.